Resistin and GFR

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To the Editor: Recently, Axelsson *et al.*[1] showed that glomerular filtration rate was consistently associated with serum resistin levels in patients with chronic kidney disease. It was found that the significant relationship between plasma resistin levels and insulin resistance was lost after adjustment for glomerular filtration rate, leading to the conclusion that renal function is an important factor to take into account when relating insulin sensitivity to inflammatory biomarkers in patients with kidney disease or diabetes mellitus. We have data from a population-based cohort of 64-year-old women, consisting of women with known and new diabetes (diabetes mellitus, $n=229$), impaired glucose tolerance ($n=210$), and normal glucose tolerance ($n=191$).[2] Diabetes mellitus, impaired glucose tolerance, and normal glucose tolerance were defined according to the World Health Organization classification. The serum levels of resistin were measured with an enzyme-linked immunosorbent assay kit (R&D Systems Europe, Abingdon, UK). The characteristics of the subjects are presented in Table 1. Serum creatinine did not differ between the groups and correlated positively to serum resistin (Spearman's correlation coefficients 0.36 ($P<0.01$), 0.28 ($P<0.01$), and 0.15 ($P<0.05$) for the diabetes mellitus, impaired glucose tolerance, and normal glucose tolerance groups, respectively). In a multivariate analysis, serum creatinine remained associated with resistin after adjustment for C-reactive protein, white blood cell count, high-density lipoprotein cholesterol, body mass index, glucose tolerance group, and plasma insulin (partial correlation coefficient 0.33, $P<0.001$). These data indicate that the association between glomerular filtration rate and serum resistin also represents a physiological mechanism that not necessarily is linked to kidney disease.

Table 1 | Characteristics of the subjects (geometric means ± s.d.) (*n*=630)

	DM (*n*=229)	IGT (*n*=210)	NGT (*n*=191)
Serum resistin (ng/ml)	10.8±3.6	10.2±3.7	9.9±3.2**
Serum creatinine (μmol/l)	89±14	89±11	89±10
BMI (kg/m^2)	28.8±4.9	27.1±5.0	25.8±3.5*
Blood glucose (mmol/l)	7.1±2.8	5.0±0.6	4.7±0.5*
Serum HDL cholesterol (mmol/l)	1.45±0.43	1.56±0.42	1.74±0.42*
White blood cell count (× 10*9/l)	6.6±1.8	6.1±1.8	5.6±1.5*
C-reactive protein (mg/l)	1.9±10.3	1.3±3.7	1.3±2.5*

Abbreviations: BMI, body mass index; DM, diabetes mellitus; HDL, high-density lipoprotein; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; s.d., standard deviation.
*$P<0.001$; **$P=0.006$.

1. Axelsson J, Bergsten A, Qureshi AR *et al.* Elevated resistin levels in chronic kidney disease are associated with decreased glomerular filtration rate and inflammation, but not with insulin resistance. *Kidney Int* 2006; **69**: 596–604.
2. Brohall G, Behre CJ, Hulthe J *et al.* Prevalence of diabetes and impaired glucose tolerance in 64-year-old Swedish women. *Diabetes Care* 2006; **29**: 363–367.

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Is there a link between inflammation, plasma resistin levels, and protein malnutrition in hemodialysis patients?

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To the Editor: Similarly to the article by Axelsson *et al.*[1] entitled 'Elevated resistin levels in chronic kidney disease are associated with decreased glomerular filtration rate and inflammation, but not with insulin resistance' we have recently observed in 33 non-diabetic hemodialysis patients that elevated resistin plasma levels are not associated with insulin resistance. In addition, we detected for the first time in human subjects that resistin levels are inversely correlated with the protein catabolic rate ($r=-0.416$, $P=0.025$), which is known to parallel the dietary protein uptake (Figure 1).[2] Axelsson *et al.*[1] have not reported on this important aspect in their manuscript despite the high prevalence of protein and energy malnutrition in hemodialysis patients and in patients with chronic kidney disease.

The finding by Axelsson *et al.*[1] that plasma resistin levels are strongly correlated with inflammatory markers and

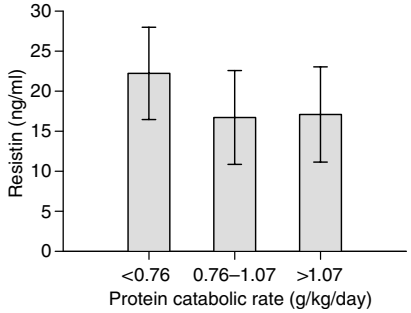

Figure 1 | Hemodialysis patients ($n=33$) were divided into three groups of 11 patients each according to the protein catabolic rate. The patients with the lowest protein catabolic rate exhibited the highest resistin levels. These intergroup differences are statistically significant ($P<0.05$).

independent from glomerular filtration rates is of considerable interest, as elevated resistin levels in various other disorders have been associated with both inflammation as well as malnutrition.[3–5]

Taking into account that inflammation has been closely related to malnutrition and in particular to protein–energy malnutrition,[6] one may assume that there is a relationship between inflammation, plasma resistin levels, and protein malnutrition in hemodialysis patients and in patients with chronic kidney disease that is yet to be clarified.

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Response to 'Resistin letters'

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We thank Fagerberg *et al.* for their contribution to the growing body of evidence refuting a causative relationship between the protein resistin and insulin resistance in man.[1] Indeed, resistin was first described as found in inflammatory zone (FIZZ)-1, indicating its structural similarity to several other proinflammatory cytokines.[2] Indeed, resistin is expressed mainly in immunocompetent cells such as leukocytes, and not in adipocytes as had previously been thought.[3,4]

Given the fact that even a mild renal function impairment is associated with a chronic low-grade inflammation[5] and a markedly increased risk of cardiovascular death, it is not surprising that the patients in the study of Fagerberg *et al.* displayed increased resistin levels that were also correlated with serum creatinine, C-reactive protein, and leukocyte counts.

Taken together, we believe that this study further underscores the relationship between decreasing renal function and increased risks of inflammation and cardiovascular disease. Resistin is one part of this complex, where we are still looking for a unifying mechanism and an effective therapy.

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Enlightenment on liver lanthanum exposure

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To the Editor: Tissue lanthanum concentrations in the paper by Slatopolsky *et al.*[1] are similar to our own and others' findings,[2] but have been interpreted very differently. Comparisons with 'untreated' controls are used to highlight 'marked' and 'striking' increases in deposition in nephrectomized rats, including a 98-fold increase in liver concentration. When the appropriate comparator is used (lanthanum-treated rats with normal renal function), there is no statistical increase in bone and kidney concentrations in the uremic animals, and only two- to three-fold higher liver concentrations after 15 weeks of treatment. This is entirely consistent with the absence of any effect of renal failure on systemic lanthanum exposure[3] and a small (two- to three-fold) increase in first-pass liver exposure, as reported recently for this uremic model.[2] Although tissue concentrations increased over time (termed 'progressive accumulation'), their study was too short to fully reflect the tissue kinetics of lanthanum, and longer-term studies suggest achievement of steady-state conditions (Figure 1). Although a maximal dose of lanthanum (3% (w/w) of diet, 15–22 times the human dose of 3 g/day)[1] was administered for as long as practicable in a nephrectomized model (limited by death owing to renal failure), lanthanum concentrations were still only at trace levels (<3 p.p.m.). As the natural liver concentrations of other lysosomally transported metals such as iron and copper are up to 2007 and 55 p.p.m., respectively,[4] there would